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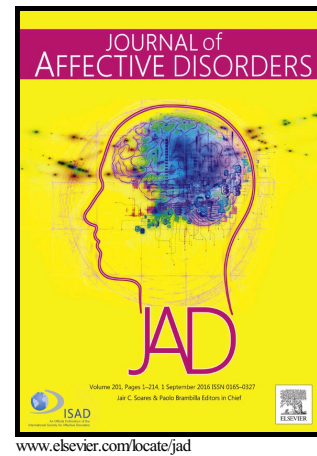
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**Screening for anxiety, depression, and anxious depression in primary care: A
field study for ICD-11 PHC**

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Abstract**Background:**

In this field study of WHO's revised classification of mental disorders for primary care settings, we tested the usefulness of two five-item screening scales for anxiety and depression to be administered in primary care settings.

Methods:

The study was conducted in primary care settings in four large middle-income countries. Primary care physicians (PCPs) referred individuals who they suspected might be psychologically distressed to the study. Screening scales as well as a structured diagnostic interview, the Clinical Interview Schedule, Revised (CIS-R), adapted for proposed decision rules in ICD-11 PHC, were administered to 1,488 participants.

Results

A score of 3 or more on one or both screening scale predicted 89.6% of above-threshold mood or anxiety disorder diagnoses on the CIS-R. Anxious depression was by far the most common CIS-R diagnosis. However, there was an exact diagnostic match between the screening scales and the CIS-R in only 62.9% of those with high scores.

Limitations

This study was confined to those in whom the PCP suspected psychological distress, so does not provide information about the prevalence of various mental disorders in primary care settings.

Conclusions

The two five-item screening scales for anxiety and depression provide a practical way for PCPs to evaluate the likelihood of mood and anxiety disorders without paper and pencil measures that are not feasible in many settings. These scales may provide substantially improved case detection as compared to current primary care practice, and offer a realistic alternative to complex diagnostic algorithms used by specialist mental health professionals.

Key words: Anxiety; Depression; Primary Care; Screening; ICD-11

The World Health Organization (WHO) is preparing a revised version of the classification of mental disorders for primary health care (ICD-10 PHC; WHO, 1996) as part of the 11th revision of the International Classification of Diseases. Proposals for a new primary care classification have been developed by a working group comprising equal numbers of primary care physicians (PCPs) with a special interest in mental disorders and mental health professionals engaged in teaching mental health skills to PCPs. A separate classification of mental disorders for primary care is needed because the parent classification provides a poor fit to common mental disorders as presented in primary care settings (Gask, Klinkman, Fortes, & Dowrick,

2008), which are often in an earlier and less severe form than those seen by mental health professionals (Goldberg, 2011). Existing specialist mental disorders classifications (American Psychiatric Association, 2013; WHO, 1992) tend to ignore anxiety symptoms unless they have lasted for several months, while depressive episodes can be diagnosed after a period of two weeks. Yet many depressed people are also currently anxious (Goldberg, Prisciandaro, and Williams, 2012), and consistent differences between depression with and without anxious symptoms have been found in studies that have examined the specific contribution of anxiety to clinical status (Fava et al. 2008; Goldberg & Fawcett, 2012; Goldberg, Wittchen, Zimmerman, Pfister, & Beesdo-Baum, 2014). It is important for PCPs to take account of the patient's clinical state at the time when treatment is sought, and to be aware of differences in ease of treatment, clinical outcome, and suicidal risk.

As proposed, the revised primary care classification for ICD-11 Mental and Behavioural Disorders (ICD-11 PHC) considers *anxious depression* to be an important form of depressive episode in general medical practice (Goldberg 2014; Silverstone & von Studnitz, 2003), diagnosed when the patient satisfies requirements for both current anxiety and depression, using the same 2-week duration requirement for both. Goldberg and Fawcett (2012) argued that when depression is accompanied by current anxiety, the risk of suicide is greater and the course of illness is less responsive to treatment. Such patients often also present with somatic complaints. In the proposed ICD-11 PHC, *depressive episode* also requires a duration of 2 weeks, and should be diagnosed when there are no or few symptoms of anxiety; conversely,

current anxiety should be diagnosed when anxiety symptoms have persisted for more than 2 weeks but there are few or no symptoms of depression.

Goldberg and colleagues (2012) used data from a previous WHO study of mental disorders in general medical and primary care settings in 14 countries (Üstün & Sartorius, 1995) to show that the correlation between anxious and depressive symptoms was +0.88 and that anxious depression is much more common in primary care settings than “co-morbid generalized anxiety and depression”, where the individual meets the diagnostic requirements of both a depressive episode and generalized anxiety disorder using a duration requirement of 6 months for anxiety symptoms. Kessler and his colleagues have confirmed that briefer durations of anxiety are predictive of subsequent psychopathology and have just as much associated disability at 6-month follow-up as longer durations (Kessler et al., 2005; Ruscio et al., 2007). In addition, *subclinical mixed depression and anxiety*, in which significant symptoms of both anxiety and depression are present but neither set of symptoms satisfies diagnostic requirements for depression or an anxiety disorder, has been shown to be a major cause of psychiatric morbidity in primary care settings. In the UK, it has been shown to account for 20.3% of all time off work, as compared to depression, which only accounts for 8.2% (Das-Munshi et al., 2008).

Definitions based on the above descriptions were submitted to a range of experts on mental disorders in primary care settings around the world, and focus groups were conducted in eight countries (Lam et al., 2013) in order to obtain the views of working PCPs and nurses on the proposed changes to the ICD-10 PHC classification. The proposal for a new category of anxious depression was universally

welcomed by the primary care professionals participating in the focus groups.

Depressive and anxiety disorders have been repeatedly established as very common in primary care settings in studies conducted in a range of countries around the world (see, for example, King et al., 2008; Kroenke, Spitzer, Williams, Monahan, & Löwe, 2007; Pothan, Kuravilla, Philip, Joseph, & Jacob, 2003; Spiers et al., 2016; Üstün & Sartorius, 1995). In spite of the prevalence and importance of these conditions in primary care and their substantial contribution to disability (Whiteford et al., 2013), rates of identification and treatment remain very low, with less than half of depressive episodes correctly identified even in high-resource primary care settings (Mitchell, Vaze, & Rao, 2009). PCPs are under ever-increasing time pressure; there are competing demands for the clinician's attention during encounters that typically last only a few minutes, and there is insufficient time to address each demand (Klinkman, 1997). Even mental health specialists have difficulty remembering the complex diagnostic algorithms for mood disorder in current diagnostic systems (Zimmerman, Chelminski, McGlinchey, & Young, 2006). Therefore, PCPs are in great need of feasible and accurate screening procedures for depression and anxiety. However, existing paper and pencil screening tests are not available or appropriate in many global settings for reasons of language or literacy. These difficulties are likely to be even more pronounced in low- and middle-income countries, where more than 80% of the world's population lives. This study tested very brief assessments of depression and anxiety consisting of only a minimal number of additional questions designed to be asked directly by the PCP, thus minimizing the additional time required in the patient encounter and obviating the need for paper and pencil tests and

instrument scoring. In addition, these screening questions were tied directly to the proposed diagnostic guidelines for depression and anxiety in the ICD-11 PHC.

Brief candidate screening scales for depression and anxiety had been derived from an earlier WHO study of psychological disorders in primary care carried out in 14 countries (Üstün & Sartorius, 1995). In this study, a stratified random sample of 5,438 primary care patients had been assessed using DSM-III-R criteria for common mental disorders, but with the duration requirement for a diagnosis of anxiety disorder reduced to one month. From these symptom data, five-item screening scales for depression and anxiety were derived using item response theory (Goldberg et al., 2012). The sensitivity of the five-item depression scale for major depression was found to be 90% and specificity 88.5%, while for generalised anxiety disorder sensitivity of the five-item anxiety scale was found to be 79.8% and specificity 72.5% (Goldberg et al. 2012).

The aim of the present study was to evaluate the ability of these two brief screening scales to identify cases of depression and anxiety in primary care settings in four large middle-income countries (Brazil, China, Mexico, and Pakistan) in order to consider their potential usefulness to global PCPs in arriving at a preliminary assessment. To minimize necessary PCP time for administration, each scale was structured so as to consist of two screening questions and an additional set of three questions to be asked if either of the screening items was positive. A related aim was to determine the best threshold scores on these scales for detecting ICD-11 cases of depression and anxiety. The results of the screening scales were compared with a structured psychiatric interview designed for use in the general population, the revised

Clinical Interview Schedule (CIS-R: Lewis, Pelosi, Araya, & Dunn, 1992), adapted according to the proposals for ICD-11 PHC to use a duration requirement of only 2 weeks for current anxiety, to yield a diagnosis of anxious depression when patients met the requirements of both current depressive episode and current anxiety, and to yield a diagnosis of subclinical mixed depression and anxiety to patients who had significant symptoms of both depression and anxiety but did not meet the full diagnostic requirements of either disorder separately.

Methods

The present field study was carried out in primary care settings in Brazil (São Paulo and Rio de Janeiro), the People's Republic of China (Hong Kong), Mexico (Zapopan), and Pakistan (Rawalpindi). These are large lower and upper middle-income countries in diverse regions of the world, representing a substantial portion of the global population and encompassing multiple languages and wide cultural variations. Centers were selected based on local investigator interest and ability to identify institutional resources in order to complete the study.

The point of the present study was not to examine the prevalence of depressive and anxiety disorders in primary care settings, which has been the focus of other studies. Rather, the study used a cross-sectional descriptive design in a population of patients who were suspected by their PCPs of possibly being psychologically distressed. This procedure was used in order to create an enriched sample in whom a psychological disorder was more likely in order to be able to examine the relationship between two brief screening instruments and diagnoses

produced by the detailed psychiatric interview, as well as to replicate the conditions under which PCPs would be most likely to consider screening for such conditions. PCPs were asked to use a relatively low index of suspicion for inclusion in the study in order to include a sufficient proportion of non-cases in order to be able to examine the performance of the scales in differentiating cases from non-cases. The study was administered in the local language of each participating country, with back translation and comparison by the researchers with the original English language version. The protocol for the study (available from the Psychiatry Research Trust's website, <http://www.psychiatryresearchtrust.co.uk/protocols/worldhealth.pdf>) was approved by both the WHO Research Ethics Review Committee and the appropriate local Institutional Review Board at each participating center.

At each center, the collaborating Local Investigator (LI) assembled a group of local PCPs who agreed to participate. At a preliminary meeting with PCPs who were potentially interested in participating in the study, the LI reviewed the study procedure and, using a set of slides provided by WHO, reminded PCPs of aspects of patients' behavior that might alert them to the possible presence of psychological distress.

Participants

Participants were patients being seen for primary care visits as a part of usual care in one of the participating centers, who were at least 18 years of age and whose PCP suspected might be psychologically distressed. Participating PCPs asked patients they considered to meet these criteria if they were interested in participating

in the study, which the PCP explained would involve undergoing a detailed interview administered by a research assistant.

Procedure

For patients who agreed to participate, the PCP completed a Patient Encounter Form, which included the two five-item screening scales for depression and anxiety shown below. PCPs were asked to administer the two preliminary screening questions for each scale, and only if they obtained a positive answer to either screening question to ask the remaining three questions. As noted above, the purpose of the two screening questions was to save time, given that PCPs often have only a few minutes for each patient. On the Patient Encounter Form, PCPs also rated their view of the level of disability and distress associated with the mood and anxiety symptoms, whether a diagnosable disorder according to the new proposed guidelines was present, and the severity of the disorder. Very general but non-identifying demographic information (gender and age group) was recorded for patients who declined to participate in the study, as well as their reason for refusal.

Brief screening scales for depression and anxiety

Five-item depression scale:

Screening items:

D1 Have you been feeling depressed every day for the past 2 weeks?

- D2 During the past two weeks, have you experienced less interest or pleasure from activities?

Additional items (to be asked if positive response to either screening item):

- D3 During the past two weeks, have you experienced poor concentration?
- D4 During the past two weeks, have you experienced feelings of worthlessness?
- D5 During the past two weeks, have you felt you wanted to die or had thoughts of death?

Five-item anxiety scale:

Screening items:

- A1 Have you felt nervous or anxious during the past 2 weeks?
- A2 During the past 2 weeks, have you found that you are not able to control your worrying?

Additional items (to be asked if positive response to either screening item):

- A3 During the past 2 weeks, have you had trouble relaxing?
- A4 During the past 2 weeks, have you felt so restless it was hard to keep still?

A5 During the past 2 weeks, have you felt afraid that something awful might happen?

Consenting patients were interviewed by a research assistant who was not aware of the PCP's evaluation beyond the suspicion of psychological distress, using a computerized version of the CIS-R. Patients were interviewed during the same visit if possible or during a scheduled return visit. The diagnostic interview had been adapted to make proposed ICD-11 diagnoses using the diagnostic requirements described earlier in this article. These adaptations consisted of using a duration requirement of only 2 weeks for current anxiety, assigning a diagnosis of anxious depression to patients who met the requirements of both current depressive episode and current anxiety, and assigning a diagnosis of subclinical mixed depression and anxiety to patients who had significant symptoms of both depression and anxiety but did not meet the full diagnostic requirements of either depression or current anxiety.

Data analysis

The primary measures used in the study were the two five-item screening scales for depression and anxiety shown above, and mood and anxiety disorder diagnoses produced by the CIS-R, using diagnostic algorithms consistent with the proposed ICD-11 PHC, as described above. The screening scales were scored as the number of positive items for depression, hereafter referred to as the Dep5 score, and the number of positive items for anxiety, referred to as the Anx5 score. Prediction of CIS-R diagnoses using the screening scales was assessed based on percentage of true cases with high scores and percentage of non-cases with low scores, and positive

predictive values (PPVs) and negative predictive values (NPVs) derived from ROC curves. PPVs and NPVs were calculated using the formula for general use provided Altman and Bland (1994) adapted by using country-specific values for the percentage of cases and non-cases correctly identified and the overall prevalence in the four countries. Optimized cutoff scores were selected using the Youden index (Youden, 1950; see López-Ratón, Rodríguez-Álvarez, Cadarso-Suárez, & Gude-Sampedro, 2014).

The descriptive analyses for this study consisted of frequencies and proportions for socio-demographic and clinical characteristics by countries or by diagnostic groups. Between-group differences in frequencies (proportions) were tested using Chi-square analyses. For frequency data, pairwise comparisons among values where the overall Chi-square test reached a significance level of $p < .05$ were corrected for multiple family-wise comparisons using the Holm correction and a significance parameter of $p < .05$. For interval variables, mean, standard deviation, and 95% confidence intervals were calculated. Overall significance was tested using one-way analyses of variance (ANOVA), and pairwise comparisons among values where the overall test reached a significance level of $p < .05$ were corrected for multiple family-wise comparisons using the Bonferroni correction and a significance parameter of $p < .05$.

The management and modeling of statistical data for ROC curves was performed using STATA software Version 12. The calculation of the Youden index and the analyses of differences between groups for proportions were performed using

R statistical software Version 3.1.3. Other analyses were performed using SPSS software Version 19 and STATA.

Results

A total of 1,697 patients were approached to participate in the study because their PCPs suspected psychological distress. Of these, 41 patients declined to participate in the study because they did not have time (32%), were too ill (17%), preferred not to (20%), or for other reasons (31%). There were no difference by gender or age group between those who agreed and those who declined to participate in the study. Of the 1,656 patients who agreed to participate in the study, 153 patients did not complete the interview (e.g., because they did not attend a separate interview appointment). Data recording problems required the exclusion of 15 participants from the analyses, so the final sample consisted of 1,488 patients with complete data. There were no significant differences by gender, age, scores on the anxiety and depression scales, or on PCP-rated disability, distress, or disorder severity between the 153 non-completers and the 1,488 patients included in the final sample.

The overall demographic characteristics of the sample by country for gender and age, as well as scores on the depression and anxiety screening scales (referred to as Dep5 and Anx5) are shown in Table 1. There were significant differences among countries on all variables shown in Table 1. A higher proportion of the Chinese sample was male (29.2%) than for other countries. On average, participants from Pakistan were youngest and participants from China were oldest. Mexican and Pakistani participants had the highest average scores on the Dep5, and Chinese

participants the lowest, while participants from Brazil and Mexico had the highest average scores on the Anx5, and again participants from China had the lowest.

Table 2 shows the diagnostic results of the CIS-R by country and overall. Of the 1,488 participants in the study, 310 (20.8%) had no mood or anxiety disorder diagnosis, and 40 (2.7%) had only subclinical mixed depression and anxiety on the CIS-R. The remaining 1,138 participants (76.5%) were judged by the CIS-R to have one of the three main diagnoses of current anxiety, depression (non-anxious), or anxious depression. In all countries, anxious depression was the most common disorder, accounting for 725 of the 1138 participants (63.7%) with an above-threshold CIS-R diagnosis (i.e., not counting subclinical mixed depression and anxiety), compared with 26.1% with current anxiety ($n = 297$), and 10.2% ($n = 116$) with non-anxious depression. The rates for current anxiety were highest in Brazil and Mexico, and lowest in Pakistan. Rates for anxious depression were highest in Mexico and Pakistan and lowest in China.

Table 3 shows the country-specific diagnostic accuracy of the five-item depression screening scale (Dep5) in detecting cases of both (non-anxious) depression and anxious depression, using the CIS-R as a standard. For a clinician, the most important properties of a screening scale are the probability that a person with a high score is a case (i.e., PPV) and its tendency to correctly identify non-cases (i.e., NPV). Cutoff scores were selected using the Youden index (Youden, 1950), based on the optimum trade-off between the percentage of cases correctly identified and percentage of non-cases correctly identified (López-Ráton et al., 2014). The country-

specific cutoff score for case identification was 2 for China and 3 for all other countries.

Table 4 shows the overall diagnostic accuracy of the five-item anxiety scale in detecting cases of current anxiety and anxious depression. In China and Pakistan, the best threshold for case identification was a score of 2, in Mexico it was 3, and in Brazil it was 4.

Table 5 combines the data from the four participating countries, calculating an overall value for the relationship between the two five-item screening scales and diagnoses of depressive and anxiety disorders according to the CIS-R. Across countries, the best cutoff for case identification for both scales across countries was a score of 3.

As noted, the PPVs and NPVs shown in Tables 3 through 5 have been calculated using Altman and Bland (1994) formula for general use, which tends to yield higher values. For example, for the depression screening scale, the corrected PPV for a cutoff of 3 as shown in Table 5 is 0.88 in contrast to an uncorrected value of 0.70. The corresponding figures for the anxiety screening scale are 0.89 (shown in Table 5) and 0.78.

Table 6 shows the relationship between diagnostic groupings obtained based on the two five-item screening scales and specific diagnoses on the CIS-R. Using a cutoff of 3 on both scales (see Table 5), the screening scales correctly classified as cases or non-cases 84.0% ($CI_{95} = 82.1\% - 85.9\%$; $n = 1250$) of the 1488 participants, including 1020 high scorers with an above threshold diagnosis, and 230 low scorers

without one. The screening scales correctly identified 89.6% ($CI_{95} = 87.9\% - 91.4\%$; $n = 1020$) of the positive cases and 65.7% ($CI_{95} = 60.7\% - 70.7\%$; $n = 230$) of the non-cases. However, 11.4% ($CI_{95} = 8.8\% - 14.8\%$; $n = 40$) of the non-cases included in this figure were identified as having subclinical mixed depression and anxiety by the CIS-R, and if these cases are excluded correct negative case identification was 71.0% ($CI_{95} = 65.9\% - 76.0\%$; $n = 220$). When individuals with elevated scores on the screening scales were assigned no diagnosis on the CIS-R, it was generally because duration or functional impairment requirements had not been met for an above-threshold clinical diagnosis.

In spite of the very high correlation between depressive and anxious symptoms observed in previous studies (Goldberg et al., 2012), the use of both screening scales increased the accuracy of case identification. Using only the Dep5, the number of CIS-R cases detected dropped to 798 (70.1%; $CI_{95} = 67.5\% - 72.8\%$) of the 1138 participants with above-threshold diagnoses on the CIS-R, in contrast to 1020 cases (89.6%; $CI_{95} = 87.9\% - 91.4\%$) detected using the Dep5 and Anx 5 together. (See Table 6.)

The screening scales were not as accurate in assigning specific mood and anxiety disorder diagnoses. In only 62.9% of cases with scores of 3 or more on one or both screening scales ($CI_{95} = 60.0\% - 65.9\%$; $n = 642$) was there an exact match between the results of the screening scales and the CIS-R diagnosis.

Discussion

Participants in the current study were patients seen in primary care visits in centers in four middle-income countries in different parts of the world with different languages and broad cultural variation whose PCPs suspected that they might be psychologically distressed. The two brief screening scales proposed here were able to identify 89.6% ($CI_{95} = 87.9\% - 91.4\%$) of individuals in this sample who had current anxiety, depression or anxious depression on a structured diagnostic interview. This is a substantial improvement in case identification as compared with available evidence related to current primary care practice (Mitchell et al., 2009). This was accomplished using a very low-burden screening that could be feasibly implemented in the context of a wide range of global primary care settings.

These screening scales do not require the memorization of complex diagnostic algorithms that are used by mental health specialists, which may be difficult for PCPs to remember and apply (Krupinski and Tiller 2001; Rapp and Davis 1989). The screening scales also provide a useful alternative for global primary care settings to paper and pencil screening instruments, which may not be available or may not be practical for reasons of language or literacy. The screening scales therefore offer a substantially more practical alternative for implementation in low-resource settings. Given time and resource pressures, they may also be of considerable value in high-income countries.

Among the patients suspected by their PCPs of being psychologically distressed who participated in this study, when the long duration requirement for a

diagnosis of anxiety was removed, anxious depression was by far the most common of the group of mood and anxiety disorders. The proposed classification draws attention to the distinction between individuals with depression who do and who do not have concurrent anxiety. This study affirms the relevance of this approach in global primary care settings, as did the results of our earlier focus group study (Lam et al., 2013). These two presentations of depressive illness have important implications for management and course of illness (Goldberg, 2014; Goldberg et al., 2014; VanValkenberg, Akiskal, Puzantian, & Rosenthal, 1984), but the distinction is seldom made in clinical practice.

The performance of the screening scales in identifying 89.6% ($CI_{95} = 87.9\% - 91.4\%$) of individuals with an above-threshold depressive or anxiety disorder is in contrast to their ability to provide a precise diagnostic assessment among those who had high scores (62.9%; $CI_{95} = 60.0\% - 65.9\%$). However, we know that common mental disorders merge into one another, without sharp borders between them. Research in primary care settings has demonstrated that there is a large common component that underlies the allegedly different syndromes of common mental disorders (Löwe, Spitzer, Williams, Mussell, Schellberg, & Kroenke, 2008; Simms, Prisciandaro, Krueger, & Goldberg, 2012). Thus, anxiety and depression are by no means distinct, and the presence of both types of symptoms has significant implications for primary care management. The imperfect relationship between the exact diagnostic assessment by the two five-item scales and the CIS-R diagnoses using full information probably should be understood in terms of the common variance between allegedly different mental disorders, and continuity in the two

underlying variables at the cases/non-case threshold (Simms et al. 2012). At the same time, the most accurate identification of above-threshold CIS-R cases was obtained using both the depression and anxiety screening scales together (see Table 6).

It is clear from the wide range in proportions of individuals with no depressive or anxiety disorder diagnosis across the four countries (Table 2) that there may be population differences among countries or among clinical settings, or among the thresholds for what might constitute a psychological disorder that should be applied by PCPs in a given setting. This relates to a potential difficulty in applying a single screening threshold across the world. We have calculated values that combine data for all four countries (Table 5), but it may be preferable to use country-specific values (Tables 3 and 4) in implementing the scales in any particular context.

The questions used in the present study were derived from an analysis of data from general medical and primary care settings in 14 different countries (Goldberg et al., 2012), but it may still be necessary to take account of local variations. It has previously been demonstrated that cutoff points for a screening questionnaire can vary according to demographic characteristics of the population under study (Goldberg, Oldehinkel, & Ormel, 1998; Mari & Williams, 1986). For example, the lower cutoff scores for China on both scales (Tables 3 and 4) may reflect demographic differences, culturally based reluctance to report psychological symptoms, the fact that the Chinese sample was older, or the higher proportion of males in the Chinese sample (Mari & Williams, 1986).

The greater variability in cutoff scores for the anxiety screening scale (Table 4) may suggest that these items could be relatively more susceptible to such influences. Indeed, recent studies have found that screening tools such as the 7-item Generalized Anxiety Disorder scale (GAD-7) can be culturally dependent and may require cultural adaptation in different contexts (Barthel, Barkman, Ehrhardt et al., 2014; Parkerson, Thibodeau, Brandt et al., 2015; Sousa, Viveiros, Chai et al., 2015). These issues will require further research.

Limitations

An important limitation of the study is that it was not designed as a prevalence study, and therefore does not contain information on patients whose PCPs do not consider them to exhibit psychological distress. Thus, the preceding discussion of the proportion of cases correctly identified by the screening scales in this sample is by no means the same as the sensitivity of the screening questions among all primary care patients, and in this sense is likely to be somewhat optimistic. In contrast, the proportion of non-cases correctly identified in this sample is likely to be pessimistic, as many non-cases are easy to identify and would not have been approached to participate in this study. Our methodology was designed to be as non-intrusive as possible for administration in busy clinical settings in the four participating middle-income countries. Clearly, the centers participating in this study may not constitute a representative sample of their countries, and these countries do not constitute a representative sample of the whole world, but they do represent a substantial proportion of the world's population and diverse languages, global regions, and primary care population characteristics. We hope that these results will encourage

other countries to apply and assess the proposed ICD-11 PHC classification of anxiety and depression and the related proposed screening tools and thereby contribute further to the evidence base in this area.

Conclusions

Mood and anxiety disorders are responsible for high proportions of global disease burden and disability (Whiteford et al., 2013) and are vastly undertreated (WHO World Mental Health Survey Consortium, 2004). Most people who suffer from these conditions will never see a mental health specialist, particularly in low- and middle-income countries (Kohn, Saxena, Levav, & Saraceno, 2004). For them, primary care settings currently represent the best hope for appropriate identification and treatment (World Health Organization, 2013; 2016).

The full decision rules that underlie the specialist classifications of mental disorders cannot be applied in primary care settings; there is not enough time and PCPs have other important priorities in detecting other health conditions. Even in high-income countries, there are considerable pressures on time and resources in primary care settings, and limited options for specialist referral for common conditions. The revised ICD-11 PHC classification presents a more realistic set of descriptions of psychological disorders as they present in primary care. The screening scales tested in the current study have the potential to provide major improvements in case detection through a procedure that can be feasibly incorporated into global primary care practice.

While the screening scales cannot make definitive diagnoses, they can direct attention to the relative importance of anxious and depressive symptoms in determining the patient's present state. The dimensions that underlie the two screening scales (i.e., depressive symptoms and anxious symptoms) are clinically useful in that they are associated with specific treatment approaches that can be appropriately implemented in primary care settings (Goldberg, Bridges, Duncan-Jones, & Grayson, 1987). This is not intended to imply that above-threshold cases need pharmacological treatment. Primary care management guidelines developed by WHO (WHO, 2016) include a variety of evidence-based behavioral activation and psychosocial intervention strategies as well as medications that can improve the lives of individuals with mood and anxiety disorders as a part of a comprehensive set of strategies to reduce the global burden of mental disorders (WHO, 2013).

Conflicts of Interest

All authors have completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and declare that they have no potential conflicts of interest to report, except that Linda Gask reports personal fees from Takeda Pharmaceuticals during the conduct of this study.

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Table 1. Characteristics of 1,488 participants completing the study, by country and overall

	Brazil	China	Mexico	Pakistan	Total
Female (n, %)	291 87.7% ^a	213 70.8% ^b	324 79.4% ^c	344 77.0% ^c	1,172 78.8%
Male (n, %)	41 12.3% ^a	88 29.2% ^b	84 20.6% ^c	103 23.0% ^{b,c}	316 22.2%
Age (M, SD)	48.3 ^a SD = 14.5	55.5 ^b SD = 15.4	43.3 ^c SD = 14.7	38.3 ^d SD = 13.3	45.4 SD = 15.6
Average score on Dep5 (M, SD, 95% CI)	2.5 ^a SD = 1.6 (2.3 - 2.7)	1.6 ^b SD = 1.5 (1.4 - 1.7)	3.5 ^c SD = 1.6 (3.3 - 3.6)	3.5 ^c SD = 1.3 (3.4 - 3.6)	2.9 SD = 1.7 (2.8 - 3.0)
Average score on Anx5 (M, SD, 95% CI)	3.8 ^a SD = 1.3 (3.7 - 4.0)	2.2 ^b SD = 1.4 (2.0 - 2.4)	3.5 ^a SD = 1.4 (3.4 - 3.7)	2.9 ^c SD = 1.5 (2.7 - 3.0)	3.1 SD = 1.5 (3.1 - 3.2)

Note: M = mean; SD = standard deviation; CI = confidence interval. Significant differences ($p < 0.001$) were found by country for all variables shown. Different superscripts for means or percentages across rows indicate significant differences between countries designated by different letters, adjusted for multiple comparisons.

Table 2. Number and percentages of patients in each diagnostic category based on the computerized CIS-R, by country and overall

	Brazil	China	Mexico	Pakistan	Total
	68	135	45	62	310
No diagnosis					
(n, %, 95% CI)	20.5% ^a (16.1- 24.8)	44.9% ^b (39.2 - 50.5)	11.0% ^c (8.0- 14.1)	13.9% ^{a,c} (10.7- 17.1)	20.8% (18.8 - 22.9)
Subclinical Mixed Dep & Anxiety	6	14	11	9	40
(n, %, 95% CI)	1.8% (0.4 - 3.2)	4.7% (2.3 - 7.0)	2.7% (1.1 - 4.3)	2.0% (1.0 - 3.3)	2.7% (1.9 - 3.5)
Current	88	57	94	58	297
Anxiety					
(n, %, 95% CI)	26.5% ^a (21.7 - 33.2)	18.9% (14.5 - 23.4)	23.0% ^a (18.9 - 27.1)	13.0% ^b (9.9 - 16.1)	20.0% (17.9 - 22.0)
Depression	17	23	29	47	116
(n, %, 95% CI)	5.1% (2.7 - 7.5)	7.6% (4.6 - 10.6)	7.1% (4.6 - 9.6)	10.5% (7.7 - 13.4)	7.8% (6.4 - 9.2)
Anxious depression	153	72	229	271	725
(n, %, 95% CI)	46.1% ^a (40.7 - 51.5)	23.9% ^b (19.1 - 28.6)	56.1% ^c (51.3 - 60.9)	60.6% ^c (56.1 - 65.2)	48.7% (46.2 - 51.3)
Total	332 100%	301 100%	408 100%	447 100%	1,488 100%

Note: CI = confidence interval. Significant differences ($p < 0.001$) by country were found for No diagnosis, Current Anxiety, and Anxious Depression. Different superscripts for percentages across rows for these variables indicate significant differences between countries designated by different letters, adjusted for multiple comparisons.

Table 3. Country-specific diagnostic accuracy of five-item depression scale for identifying persons with a clinical diagnosis of depression (without anxiety) or anxious depression on the CIS-R

Country	Dep5 score	N	Probability of caseness	AUC	% cases correct	% noncases correct	PPV	NPV	Youden index
Brazil	0	50	0.04	0.83	1.00	0.00	0.06		
	1	50	0.14		0.99	0.30	0.25	0.99	0.28
	2	68	0.50		0.95	0.56	0.65	0.93	0.51
	3	60	0.70		0.75	0.77	0.88	0.57	0.52
	4	71	0.77		0.50	0.88	0.94	0.33	0.38
	5	33	0.91		0.18	0.98	0.99	0.08	0.16
China	0	96	0.03	0.88	1.00	0.00	0.06		
	1	69	0.13		0.97	0.45	0.29	0.98	0.42

	2	47	0.36		0.87	0.74	0.74	0.87	0.61
	3	38	0.58		0.69	0.89	0.93	0.56	0.58
	4	30	0.77		0.46	0.97	0.98	0.33	0.43
	5	21	1.00		0.22	1.00	1.00	0.09	0.22
Mexico	0	42	0.14	0.79	1.00	0.00	0.06		
	1	53	0.34		0.98	0.24	0.23	0.98	0.22
	2	70	0.56		0.91	0.47	0.59	0.86	0.38
	3	70	0.71		0.76	0.68	0.84	0.55	0.44
	4	83	0.75		0.56	0.81	0.92	0.34	0.37
	5	90	0.92		0.32	0.95	0.99	0.09	0.27
Pakistan	0	35	0.09	0.82	1.00	0.00	0.06		
	1	17	0.12		0.99	0.25	0.24	0.99	0.24
	2	27	0.26		0.98	0.36	0.57	0.96	0.34
	3	116	0.72		0.96	0.52	0.82	0.86	0.48
	4	117	0.82		0.70	0.77	0.92	0.41	0.47
	5	135	0.93		0.40	0.93	0.99	0.10	0.33

Note: In Tables 3 – 5, ‘% cases correct’ = % CIS-R cases correctly identified using the five-item screening scale at each possible cutoff; ‘% noncases correct’ = % non-cases correctly identified; AUC = Area under curve; PPV = Positive Predictive Value; NPV = Negative Predictive Value. PPV and NPV were calculated using the formula provided by Altman and Bland (1994). Optimized cutoff scores, shaded in gray, were selected using the Youden index (Youden, 1950).

Table 4. Country-specific diagnostic accuracy of five-item anxiety scale for identifying persons with a clinical diagnosis of anxiety or anxious depression on the CIS-R

Country	Anx 5		Probability		% cases correct	% noncases correct	Youden index	
	score	N	of cases	AUC			PPV	NPV
Brazil	0	18	0.33	0.74	1.00	0.00	0.27	
	1	23	0.48		0.98	0.13	0.45	0.88
	2	28	0.43		0.93	0.26	0.72	0.65
	3	56	0.64		0.88	0.44	0.84	0.51
	4	77	0.79		0.73	0.66	0.91	0.34
	5	130	0.88		0.48	0.84	0.95	0.19
China	0	104	0.14	0.81	1.00	0.00	0.27	
	1	42	0.19		0.88	0.52	0.57	0.86
	2	43	0.47		0.82	0.72	0.85	0.67

	3	48	0.77		0.67	0.85	0.94	0.42	0.52
	4	41	0.73		0.38	0.91	0.95	0.24	0.29
	5	23	0.83		0.15	0.98	0.98	0.14	0.13
Mexico	0	26	0.31	0.78	1.00	0.00	0.27		
	1	36	0.50		0.98	0.21	0.47	0.92	0.19
	2	49	0.59		0.92	0.42	0.76	0.72	0.34
	3	62	0.85		0.83	0.66	0.89	0.53	0.49
	4	87	0.91		0.67	0.76	0.93	0.33	0.43
	5	148	0.92		0.42	0.86	0.95	0.18	0.28
Pakistan	0	93	0.40	0.69	1.00	0.00	0.27		
	1	28	0.61		0.89	0.47	0.55	0.85	0.36
	2	79	0.91		0.84	0.57	0.80	0.63	0.41
	3	53	0.83		0.62	0.63	0.85	0.32	0.25
	4	58	0.81		0.48	0.70	0.88	0.22	0.18
	5	136	0.82		0.34	0.80	0.92	0.15	0.14

Table 5. Overall diagnostic accuracy across countries of the five-item depression scale for identifying persons with a clinical diagnosis of current depression or anxious depression on the CIS-R; overall accuracy of the five-item anxiety scale for identifying persons with a clinical diagnosis of current anxiety or anxious depression on the CIS-R

Overall score across countries	N	Probability of caseness	AUC	% cases correct	% noncases correct	PPV	NPV	Youden index
Dep5 score								
0	223	0.06	0.85	1.00	0.00	0.06		
1	189	0.19		0.98	0.32	0.25	0.99	0.31
2	212	0.46		0.94	0.56	0.64	0.92	0.50

3	284	0.70		0.83	0.74	0.88	0.65	0.56
4	301	0.78		0.59	0.87	0.94	0.37	0.46
5	279	0.93		0.31	0.97	0.99	0.09	0.28
Anx5 score								
0	241	0.27	0.77	1.00	0.00	0.27		
1	129	0.42		0.94	0.38	0.52	0.89	0.31
2	199	0.67		0.88	0.54	0.79	0.69	0.42
3	219	0.78		0.75	0.68	0.89	0.44	0.43
4	263	0.83		0.59	0.78	0.93	0.29	0.37
5	437	0.87		0.37	0.88	0.96	0.17	0.26

Table 6. Relationships among diagnostic groupings based on the two five-item screening scales and specific diagnoses on the CIS-R

Screening Questions	No dx	Mixed Anx/Dep (subclinical)	Current anxiety	Non-anxious depression	Anxious depression	Total
Subthreshold	220, 63.2%	10, 2.9%	74, 21.3%	17, 4.9%	27, 7.8%	348

n, %	[58.1 - 68.3]	[2.3 - 5.4]	[17.0 - 25.6]	[2.6 - 7.2]	[4.9 - 10.6]	100%
[95% CI]						
High Anx only						
n, %	44, 15.9%	10, 3.6%	119, 43.1%	14, 5.1%	89, 32.3%	276
[95% CI]	[11.6 - 20.3]	[1.4 - 5.8]	[37.3 - 49.0]	[2.5 - 7.7]	[26.7 - 37.8]	100%
High Dep only						
n, %	21, 9.5%	10, 4.5%	28, 12.7%	38, 17.2%	124, 56.1%	221
[95% CI]	[5.6 - 13.4]	[1.8 - 7.3]	[8.3 - 17.1]	[12.2 - 22.2]	[49.5 - 62.7]	100%
High Anx & High Dep						
n, %	25, 3.9%	10, 1.6%	76, 11.8%	47, 7.3%	485, 75.3%	643
[95% CI]	[2.4 - 5.4]	[0.6 - 2.5]	[9.3 - 14.3]	[5.3 - 9.3]	[72.1 - 78.8]	100%
Total						
n, %	310, 20.8%	40, 2.7%	297, 20.0%	116, 7.8%	725, 48.7%	1,488
[95% CI]	[18.8 - 22.9]	[1.9 - 3.5]	[17.9 - 22.0]	[6.4 - 9.2]	[46.2 - 51.3]	100%

Note: For the above groupings based on the two five-item screening scales: **High Anxiety only** indicates a score of 3 or above on the Anx5 and a score of 2 or below on the Dep5; **High Depression only** indicates a score of 3 or above on the Dep5 and a score of 2 or below on the Anx5; and **High Anxiety and High Depression** indicates a score of 3 or above on the Dep5 and a score of 3 or above on Anx5.

Highlights

- Study participants presented with psychological distress to primary care physicians in 4 countries
- Two five-item screening scales for anxiety and depression were used
- Participants also received a structured psychiatric diagnostic interview
- The optimal cutoff score for both scales was 3, across four participating countries
- Screening scale scores predicted 89.6% of above-threshold mood or anxiety disorders
- This represents a major improvement in detection compared with current practice